REVIEW

Mechanisms of Drug-Induced Allergy

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We identified English-language publications on hypersensitivity reactions to xenobiotics through the PubMed database, using the search terms *drug* and/or *xenobiotic*, *hypersensitivity reaction*, *mechanism*, and *immune mediated*. We analyzed articles pertaining to the mechanism and the role of T cells. Immune hypersensitivity reactions to drugs are mediated predominantly by IgE antibodies or T cells. The mechanism of IgE-mediated reactions is well investigated, but the mechanisms of T-cell–mediated drug hypersensitivity are not well understood. The literature describes 2 concepts: the hapten/prohapten concept and the concept of pharmacological interactions of drugs with immune receptors. In T-cell–mediated allergic drug reactions, the specificity of the T-cell receptor that is stimulated by the drug may often be directed to a cross-reactive major histocompatibility complex–peptide compound. Thus, previous contact with the causative drug is not obligatory, and an immune mechanism should be considered as the cause of hypersensitivity, even in reactions that occur on primary exposure. Indeed, immune-mediated reactions to xenobiotics in patients without prior exposure to the agent have been described recently for radiocontrast media and neuromuscular blocking agents. Thus, the "allergenic" potential of a drug under development should be evaluated not only by screening its haptenlike characteristics but also by assessing its direct immunostimulatory potential.

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APC = antigen-presenting cell; Fc = fragment, crystallizable; IL = interleukin; MHC = major histocompatibility complex; p-i = pharmacological interactions of drugs with immune receptors; TCC = T-cell clone; TCR = T-cell receptor; T_{CM} = central memory T cells; T_{Eff} = effector T cells; T_{EM} = effector memory T cells

Adverse drug reactions are common and can cause serious health problems. They occur in about 10% of hospitalized patients and in about 7% of patients who require ambulatory care.[1] A widely used classification system divides hypersensitivity reactions into 2 types.[2] Type A reactions are common (80%) and are caused by the pharmacological or toxic properties of a drug. Such reactions are predictable and may occur in anyone. Type B reactions are uncommon and unpredictable and occur only in people with a certain predisposition.

Drug allergies are type B reactions that are mediated by the adaptive immune system. In practice, it is often difficult to differentiate between immune- and non–immune-mediated reactions. Because clinical signs and symptoms of most immune reactions are observed only in the elicitation phase and not in the preceding sensitization phase, the dogma has been that allergic reactions to drugs are only observed on reexposure or longer-lasting exposure (at least 3 days) to the drug. However, more recent data show that previous contact with the causative drug is not a prerequisite for immune-mediated drug hypersensitivity.[3-5] These findings indicate that the paradigm must be changed and that drug allergies might be best explained by cross-reactivity between the drug involved and other xenobiotics to which the affected patient may have been exposed beforehand.

We identified English-language publications that described hypersensitivity reactions to xenobiotics through the PubMed database, using the search terms *drug* and/or *xenobiotic*, *hypersensitivity reaction*, *mechanism*, and *immune mediated*. Articles pertaining to the mechanism of drug hypersensitivity and especially to the role of T cells in drug hypersensitivity reactions were selected for analysis. We supplemented this review with recent data describing how T cells migrate to particular tissues. Herein, we outline the current understanding of drug allergy, the mechanism of cross-reactivity, and the implications for the prevention of drug allergies (Table).

HOW DO WE BECOME SENSITIZED TO DRUGS?

Sensitization involves primary stimulation and expansion of drug-specific T lymphocytes. This may affect T cells alone or both T cells and B cells with consequent formation of drug-specific antibodies (mostly IgE).

T-CELL SENSITIZATION

Drugs are too small to elicit an immune response. Thus, to be immunogenic, they are thought to act as haptens or prohaptens. Haptens are chemically reactive small molecules (mostly <1000 D) that bind covalently to a larger protein or peptide. Prohaptens are inert drugs that undergo metabolism (bioactivation) and become reactive metabolites (haptens), which then can bind covalently to proteins.[6,7] T-cell sensitization occurs when such drug-protein

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TABLE. **Classification of Adverse Drug Reactions**

Type A (predictable in 80% of cases)	Pharmacological adverse effects Drug interactions Others	
Type B (not predictable)	Non–immune-mediated	
	Immune-mediated	Type I: IgE-mediated drug hypersensitivity Type II: IgG-mediated cytotoxicity Type III: immune complex deposition Type IV: T-cell–mediated drug hypersensitivity

complexes (hapten-carrier complexes) are taken up by antigen-presenting cells (APCs) and then transported into the local draining lymphoid tissue, where they are processed and presented on major histocompatibility complexes (MHCs). There, naïve T cells with the appropriate specificity recognize these complexes, are induced to proliferate, and expand as primed T cells.[8] Derived antigen-experienced progeny can be divided into effector T cells (T_{Eff}), which are short-lived, and effector memory (T_{EM}) and central memory (T_{CM}) T-cell subsets, which are both long-lived.[9] These T-cell subsets have distinct tissue-homing properties. Naïve T cells and T_{CM} migrate to lymph nodes, and effector T cells (T_{Eff} and T_{EM}) can interact with tissue-specific ligands.[10] Effector T cells (T_{Eff} and T_{EM}) are assumed to migrate to the location where the hapten-carrier compounds originated.

Antibody Sensitization

Hapten-carrier complexes may be antigenic for both T cells and B cells. In the presence of specific T-cell help, drug-specific B cells may proliferate and differentiate into plasma cells. Drug-specific antibodies of different isotypes are then produced. In a T-helper 2 cytokine milieu (interleukin [IL] 4, IL-5, IL-10), a class switch to IgE production may occur. In a predominantly T-helper 1 cytokine environment, production of IgG and IgM is favored.

Cross-reactivity

In addition to drug and drug-metabolite carrier compounds, drug-independent cross-reactive antigens can induce sensitizations, which can manifest as a drug allergy. The existence of such cross-reactivity is supported by recent findings. In 17 (68%) of 25 patients with cetuximab-induced anaphylaxis, IgE antibodies were found in pretreatment samples. The antibodies were shown to be specific for galactose-α-1,3-galactose,[3] which is present on the fragment antigen–binding portion of the cetuximab heavy chain and is also very similar to substances in the ABO blood group. Moreover, patients exposed to pholcodine were shown to develop IgE antibodies against pholcodine, morphine, and suxamethonium that were associated with allergy to neuromuscular blocking agents.[4] Half of the patients in that study with both clinical hypersensitivity and a positive skin test result to iodinated contrast medium were found to have reacted on primary exposure to the contrast medium without having had previous contact with it.[5] Foods and cosmetics have also been described to cause cross-reactivity with certain medications.[11]

WHAT ARE THE EFFECTOR MECHANISMS IN IMMUNE-MEDIATED DRUG HYPERSENSITIVITY?

After primary sensitization to a causative drug, a second exposure causes affected T cells and antibodies to enter the elicitation phase, corresponding to the type I to IV immune reactions (Gell and Coombs Classification). Most of the drug allergies observed are type I or IV reactions; type II and III reactions are only encountered infrequently.

IgE-Mediated Drug Hypersensitivity (Type I)

If the primary drug sensitization caused the formation of drug-specific IgE, renewed contact with small amounts of antigens (drugs) may induce symptoms. This extraordinary sensitivity is achieved by the ubiquitous presence of mast cells armed with high-affinity Fc (fragment, crystallizable) receptors (FcεRI), to which allergen-specific IgE is bound. A current paradigm postulates that an antigen must be presented in multivalent form during the elicitation phase. For an allergic reaction, allergens must bind to the fragment antigen–binding region of the IgE molecules. Binding of 2 or more cell-bound IgE molecules (cross-linking) leads to activation of the mast cell and the release of various factors, such as histamine, leukotrienes, prostaglandins, and cytokines. These molecules elicit vasodilation, increase vascular permeability, enhance mucus production and bronchoconstriction, and contribute to eosinophil recruitment. Although IgE-mediated reactions to drugs often manifest as urticaria or angioedema, they may include respiratory symptoms, shock, and severe cardiac complications. Frequently, the drugs involved in type I reactions are penicillins, cephalosporins, and neuromuscular blocking agents.

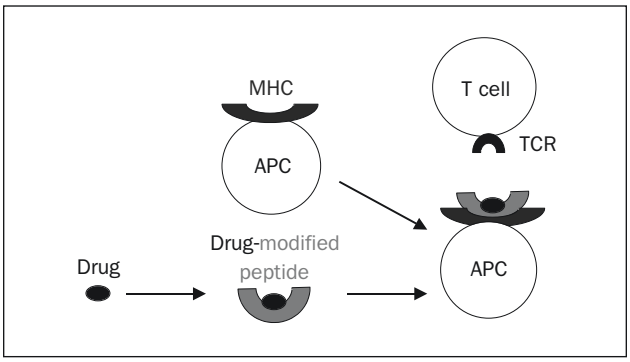

FIGURE 1. Specific T-cell recognition of drug-carrier compounds (hapten/prohapten concept). Drug/drug-metabolite carrier compounds are presented on antigen-presenting cells (APCs), where T cells with appropriate T-cell receptors (TCRs) recognize them. MHC = major histocompatibility complex.

IgG-Mediated Cytotoxicity (Type II)

Type II reactions involve IgG-mediated cytotoxicity directed to the membranes of erythrocytes, leukocytes, platelets, and probably hematopoietic precursor cells in the bone marrow. Drugs that are typically involved are methyldopa (hemolytic anemia), aminopyrine (leukopenia), and heparin (thrombocytopenia). The antibody-coated cells are sequestered to the reticuloendothelial system in the liver and spleen by Fc or complement-receptor binding. More infrequently, intravascular destruction may occur by complement-mediated lysis. Different pathways of antibody recognition of target T cells have been proposed.[12,13] In the first pathway, the structure of cell membranes is modified by the hapten and drug, which cause an immune response that is directed to these target structures. In the second pathway, the drug induces conformational changes in the structure of cell membranes, which induce nonspecific adherence to naturally occurring autoantibodies. Such reactions may occur only as long as the drug is present in soluble form.

Immune Complex Deposition (Type III)

Formation of immune complexes, a common event in a normal immune response, usually occurs without symptoms. On rare occasions, immune complexes bind to endothelial cells and lead to immune complex deposition with complement activation in small blood vessels. Why and under what circumstances an immune complex disease develops is unclear. The clinical symptoms of a type III reaction include serum sickness (eg, β-lactams), drug-induced lupus erythematosus (eg, quinidine), and vasculitis (eg, minocycline).

T-Cell–Mediated Drug Hypersensitivity (Type IV)

T-cell–mediated drug hypersensitivity may have a variety of clinical manifestations, ranging from involvement of the skin alone to fulminant systemic diseases. Frequently, the drugs involved are sulfa antibiotics and β-lactams.

HOW CAN WE EXPLAIN ALLERGIC HYPERSENSITIVITY IN THE ABSENCE OF PRIOR DRUG EXPOSURE?

Type IV effector mechanisms have not been elucidated but may be explained by the *hapten/prohapten* concept and the *pharmacological interactions of drugs with immune receptors* (p-i) concept.

The Hapten/Prohapten Concept

Drugs and their metabolites are chemically reactive and able to bind covalently to proteins. These hapten-carrier complexes are processed and presented as a stable hapten-peptide complex on the MHC of APCs in the lymph nodes and on APCs residing in the tissues (Figure 1). They are able to restimulate T cells on reexposure to the drug.[7,8] Drug-carrier compounds are recognized by effector T cells (T_{Eff} and T_{EM}) in the tissues involved or by T_{CM} in the corresponding draining lymph nodes. Whereas restimulation of effector T cells (T_{Eff} and T_{EM}) by the drug and drug derivatives presented on APCs results in local T-cell–mediated inflammation, restimulation of T_{CM} in the draining lymph nodes might be clinically manifested as an enlargement of local lymph nodes. Such events are well documented for contact dermatitis[14,15] and are also seen in some severe systemic drug hypersensitivity reactions.[16] However, the hapten/prohapten concept does not explain the allergic reactions induced by a systemically applied drug. Effector T cells (T_{Eff} and T_{EM}) are thought to migrate to the location where the prohapten or hapten-carrier compounds originated during primary sensitization,[9,10] and drug derivatives are thought to be presented predominantly at the site where they are applied (hapten drugs) or metabolized (prohapten drugs). Thus, the gastrointestinal tract (oral hapten-type drugs) or the liver (prohapten-type drugs) would be expected to be the preferred target organs for T-cell–mediated allergies. Nevertheless, immune-mediated drug-induced gastroenteritis or hepatitis are rare events, occuring much less frequently than predicted by the hapten/prohapten concept. This might be explained by a hepatic tolerance mechanism, suggesting that intrahepatic antigen presentation induces T-cell tolerance rather than sensitization.[17-20]

The p-i Concept

Investigations of drug-specific human T-cell clones (TCCs) from patients allergic to drugs revealed reactivity against the causative drug in its native form without being processed or binding to a carrier molecule. The full reactiv-

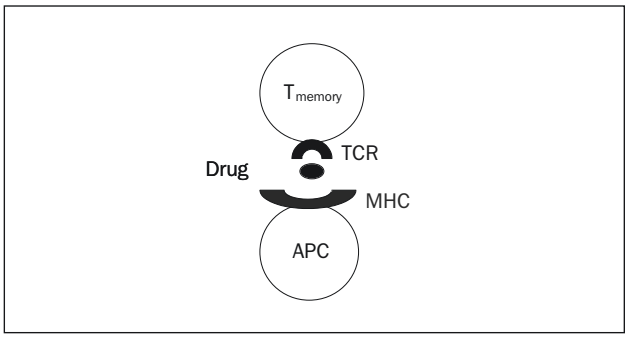

FIGURE 2. Stimulation of specific T cells by a native drug (the concept of pharmacological interactions of drugs with immune receptors). Memory T cells (T_{MEMORY}) with a certain sensitization may be stimulated by an interaction of a native drug with the T-cell receptor (TCR), supplemented by the interaction with a fitting major histocompatibility complex (MHC) molecule. APC = antigen-presenting cell.

ity of the TCCs was observed within minutes only in the presence of both the inert drug and the APC with the appropriate MHC.[21,22] The combined evaluation of the immunologic reactivity of drug-specific TCCs and the mechanism of drug "recognition" led to the development of the p-i concept (Figure 2).[23,24] Transfection of the T-cell receptor (TCR) with different antigens into mouse hybridoma cells has proven that this T-cell stimulation is dependent on the particular TCR.[25] However, the exact mechanism of this TCR-dependent T-cell activation by drugs has not been elucidated. These findings show that even poorly reactive native drugs are capable of transmitting a stimulatory signal via the TCR, which activates T cells and results in proliferation, cytokine production, and cytotoxicity.

In contrast to classic protein antigens, drugs are not confined to and concentrated in the lymph nodes and lymphatic tissues but are present throughout the body. Most drugs exert their effects in tissues and organs into which they diffuse or are transported by the circulation. If sufficient drug concentration is reached in the tissue in vivo, drugs may not only fulfill their intended activity (blocking a receptor or enzyme activity) but also interact with the adaptive immune system, particularly T cells with their highly polymorphous TCRs. Memory T cells have a lower threshold for reactivation than naïve T cells.[26,27] Thus, it is assumed, but not yet proven, that T cells that are preferentially reactivated by native drugs are previously peptide-primed memory cells. If enough cross-reactive cells are present, the reaction may occur quickly (hours to days), even on the first encounter with the drug. If the potentially drug-reactive T cells are present at low densities, previous contacts or prolonged contact may be needed to boost the reactive T-cell pool necessary for a clinically detectable reaction.

According to the p-i concept, T cells must possess 3 properties to be activated. First, the T cells must express a TCR that can bind the drug and induce a stimulatory signal. Second, the T cells must have a low threshold for activation, which allows them to react to a "minor" signal such as the drug binding to its TCR. Antigen-experienced memory T cells (T_{EM}) may have these properties. Third, an additional interaction of the TCR with the MHC on the APC must occur to enhance the response to the drug. Thus, a dense network of T cells and APCs favors such a reaction.

Recent findings indicate that these conditions are found in the skin. Effector memory T cells are highly concentrated in the skin,[28] where they may act as sentinel cells that are rapidly stimulated by antigen penetration.[29] The skin also possesses a dense network of various dendritic cells acting as APCs, predestining this organ to be affected in hypersensitivity reactions according to the p-i concept. However, the exact mechanisms of the pharmacological interactions of native drugs with TCRs have not been elucidated. In the future, it would be interesting to identify the peptide specificity of the TCRs involved.

CONCLUSION

Recent findings of preexisting sensitization in patients with cetuximab-induced or neuromuscular blocking agent–induced anaphylaxis or with hypersensitivity to iodinated contrast medium show that previous contact with the causative drug is not a prerequisite for drug allergy reactions and that these reactions may be explained by cross-reactivity. Therefore, an immune mechanism may also explain allergic reactions on primary exposure to a drug. Drug allergy due to cross-reactivity may occur in IgE-, IgG-, and T-cell–mediated reactions. The p-i concept and cross-reactivity provide an explanation for the predominant skin involvement in T-cell–mediated reactions to systemically applied drugs; skin tissue is particularly rich in memory T cells in close apposition to MHC-expressing dendritic cells.

Pharmaceutical companies developing new active substances must consider the possibility that allergic reactions to a xenobiotic may occur in the absence of prior exposure. Doing so will enable them to identify substances with high allergenic potential. Safety investigations should focus on the sensitizing potential due to haptenlike characteristics of the parent compound or metabolite. Additional early testing for p-i concept–like features of a drug and for preexisting sensitization in a broader population could help improve safety and reduce the possibility of late-phase trial failure of a drug due to its potential to produce severe allergic reactions.

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